STUDIES ON ACYL-, AROYL-, AND SULFONYL-AMINO ACID HALIDES

BY

JACK WILEY HINMAN

A. B., Grinnell College, 1941

M. S., University of Vermont, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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R. UNIV. BIBLIOTHEEK LEIDEN

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Introduction

Because of their relationship to the proteins and, more recently, to certain antibiotic substances, chemists have been interested in the chemistry of peptides. Recent work on the chemistry of penicillin has indicated that the compounds which had previously been considered as acyl- and aroyl-amino acid halides are actually the corresponding azlactone hydrohalide salts (1). Since these compounds and other closely related amino acid derivatives are important in the synthesis of peptides, a further investigation of their chemistry seemed warranted.

By 1928 it was recognized by some workers (2) that the so-called acyl- and aroylamino acid halides were readily racemized under very mild conditions. This was in contrast to the acid halides of carbobenzoxy and *p*-toluenesulfonyl derivatives of amino acids, for these derivatives have been shown to be quite stable toward racemizing influences (3). It appeared, therefore, that the racemization of the so-called acyl- and aroylamino acid halides could be explained on the basis of azlactonization, and that carbobenzoxy- and *p*-toluenesulfonylamino acid halides were not readily racemized because they were incapable of azlactone formation. Experimental verification of this postulate was sought. Studies were also made of the relative rates of azlactone formation and racemization caused by the reaction of an aroylamino acid with phosphorous tribromide, the mechanism of this reaction, and the effect of the N-substituent upon the stability of amino acid derivatives bearing a hydroxy, alkoxy, or similar group in β-position.

Discussion of Results

The N-benzoyl, N-carbobenzoxy, and N-*p*-toluenesulfonyl

derivatives of L-*p*-methoxyphenylalanine were converted to the corresponding acid halides by the action of phosphorous halides. The acid halides of the benzoyl derivative were found to spontaneously rearrange to the hydrohalide salts of 2-phenyl-4-*p*-methoxybenzyl-5-oxazolone. Treatment of this salt with diazomethane yielded the free azlactone of benzoyl-DL-*p*-methoxyphenylalanine. The azlactone and its salts were thoroughly characterized by their chemical reactions and by infrared and ultraviolet absorption spectra studies. In contrast to the behavior of the benzoyl derivative, carbobenzoxy- and *p*-toluenesulfonyl - L - *p* - methoxyphenylalanine yielded normal acid halides, which, upon treatment with diazomethane, were converted to the corresponding diazoketones. These acid halides and the compounds obtained from them retained their optical activity.

A study of the optical rotation changes which took place during the reaction of benzoyl-L-*p*-methoxyphenylalanine and one mole of phosphorous tribromide in chloroform containing a trace of ethanol indicated that the reaction involved (1) extremely rapid azlactonization of the benzoyl derivative to the optically active azlactone hydrobromide, (2) a slower reaction of the ethanol with the azlactone hydrobromide to form benzoyl-L-*p*-methoxyphenylalanine ethyl ester, and (3) a relatively much slower racemization reaction as indicated by the fact that at least 70 per cent of the azlactone was converted to the optically active ethyl ester.

The acid bromides of benzoyl-L-proline and benzoyl-N-methyl-D-phenylalanine were also found to be racemized through azlactone salt formation. The structures of the azlactone salts were established by infrared and ultraviolet absorption spectra studies and by chemical reactions. These findings demonstrated that enolization of the amide group of acyl- and aroylamino acids is not necessary for azlactonization, and that N-aroyl-N-alkylamino acids (which were previously considered incapable of azlactonization) can be racemized through azlactone salt formation. The mechanism

of the reaction appears to involve an electronic displacement from the amide nitrogen atom of the acid bromide to the bromine atom, liberating the latter as the bromide ion and conferring a full positive charge upon the nitrogen atom.

A study of the reactions of the acid halides of N-benzoyl-O-methyl-DL-serine, N-*p*-toluenesulfonylallothreonine, and α-*p*-toluenesulfonyl-β,β-diethoxy-DL-alanine indicated that elminiation of β-hydroxy and β-alkoxy groups took place only when the N-substituent would allow azlactonization and racemization to occur.

SUMMARY

It has been shown that the acid halides of benzoyl-L-*p*-methoxyphenylalanine spontaneously rearrange to form the corresponding azlactone hydrohalide salts. On the other hand, the chemical and physical properties of the acid halides of carbobenzoxy- and *p*-toluenesulfonyl-L-*p*-methoxyphenylalanine are in agreement with their classical structures.

A study has been made of the relative rates of azlactone formation and racemization in the reaction of benzoyl-L-*p*-methoxyphenylalanine with phosphorous tribromide.

A mechanism is presented for the racemization of N-aroyl-N-alkylamino acid halides.

Model studies indicate that elimination of β-hydroxy and β-alkoxy groups does not occur with N-substituted amino acid halides which are not readily racemized.

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VITA

The author was born in Pilot Mound, Iowa, June 27, 1919. He graduated from Gowrie Consolidated High School, Gowrie, Iowa, in June, 1937, and entered Grinnell College, Grinnell, Iowa, the following September. In June, 1941, he was granted the degree of Bachelor of Arts by Grinnell College. The following September he entered the Graduate School of the University of Vermont where he served as a research fellow (1941-1942) and as an instructor in the Department of Chemistry (1942-1943). In September, 1943, he was granted the degree of Master of Science by the University of Vermont at Burlington. He entered the Graduate School of the University of Illinois in October, 1943, as a special research assistant in the Department of Chemistry. From February, 1944, until October, 1945, he was a member of the OSRD group engaged in the study of the chemistry of penicillin at the Upjohn Company, Kalamazoo, Michigan. He returned to the University of Illinois in October, 1945, and since that time has held the positions of special research assistant and research fellow in the Department of Chemistry.

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